IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	SUHANI *et al.*	Atty. Dkt. No.:	RLL-349US
Serial No.:	10/549,822	Group Art Unit:	Unknown
Filing Date:	September 20, 2005	Examiner:	Unknown

Title: STABLE LAMOTRIGINE PHARMACEUTICAL COMPOSITIONS AND PROCESSES FOR THEIR PREPARATION

Certificate of Mailing

I certify that this correspondence is being deposited with the United States Postal Service as first class mail under 37 C.F.R. 1.8 and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on October 21, 2005.

Kim Campbell

Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMISSION OF PRIORITY DOCUMENT

Applicants transmit herewith a certified copy of Indian Patent Application No. 355/DEL/03 filed 21 March 2003 (21.03.2003) to which priority is claimed herein.

Respectfully submitted,

RANBAXY LABORATORIES LIMITED

By: William D. Hare
William D. Hare
Senior Counsel – Intellectual Property

Dated: October 21, 2005

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RL-349

सत्यमेव जयते

INTELLECTUAL PROPERTY **INDIA**

GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY,
PATENT OFFICE, DELHI BRANCH,
W - 5, WEST PATEL NAGAR,
NEW DELHI - 110 008.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the ***Application*** *and* ***Complete Specification*** *filed in connection with Application for Patent No.****355/Del/03*** *dated* ***21st March 2003.***

Witness my hand this 17th day of May 2004.

(S.K. PANGASA)
Assistant Controller of Patents & Designs

Drug
C07D253/075

21 MAR 2003

Govt. of India Patent Office
New Delhi
Received Rs. 5000/- in cash.
Cheque/M.O./I.P.O./D.D.,
on 21 MAR 2003
Vide Entry No. 1158 in the
Register of Valuables
Cashier

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

(See Sections 7, 54 and 135 and rule 33A)

1 We, **RANBAXY LABORATORIES LIMITED**, a Company incorporated under the Companies Act, 1956 , Corporate Office at 19, Nehru Place, New Delhi - 110 019, India

2. hereby declare –

(a) that we are in possession of an invention titled **"A PROCESS FOR THE PREPARATION OF STABLE LAMOTRIGINE TABLETS"**

(b) that the Complete Specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

3. Further declare that the inventors for the said invention are

a. SUHANI SINHA
b. KAMAL MEHTA
c. RAJEEV MATHUR
d. SANJEEV SETHI
e. RAJIV MALIK

of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India, all Indian Nationals.

4. That we are the assignee or legal representatives of the true and first inventors.

5. That our address for service in India is as follows:

DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
Plot No.20, Sector – 18,
Udyog Vihar Industrial Area,
Gurgaon – 122001 (Haryana), India.
Tel. No. (91-124) 2343126, 2342001–10; 5012501-10
Fax No. (91-124) 2342027

6. Following declaration was given by the inventors in the convention country:

We, SUHANI SINHA, KAMAL MEHTA, RAJEEV MATHUR, SANJEEV SETHI, RAJIV MALIK of Ranbaxy Laboratories Limited, Plot No. 20, Sector – 18, Udyog Vihar Industrial Area, Gurgaon–122001 (Haryana), India, all Indian Nationals, the true and first inventors for this invention in the convention country declare that the applicants herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi - 110 019, India, is our assignee or legal representatives.

a. (SUHANI SINHA)

b. (KAMAL MEHTA)

c. (RAJEEV MATHUR)

d. (SANJEEV SETHI)

e. (RAJEEV MALIK)

7. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

8. Followings are the attachment with the application:

a. Complete Specification (3 copies)
b. Drawings (3 copies)
c. Statement and Undertaking on FORM – 3
d. Fee Rs.5,000/- (Rupees Five Thousand only..) in cheque bearing No. **688457** dated :**06.03.2003** on **ANZ Grindlays Bank, New Delhi.**

We request that a patent may be granted to us for the said invention.

Dated this **21ST** day of **March, 2003.**

For Ranbaxy Laboratories Limited

(SUSHIL KUMAR PATAWARI)
Company Secretary

0355-03

21 MAR 2003

FORM 2

The Patents Act, 1970

(39 of 1970)

COMPLETE SPECIFICATION

(See Section 10)

A PROCESS FOR THE PREPARATION OF STABLE LAMOTRIGINE TABLETS

ORIGINAL

RANBAXY LABORATORIES LIMITED
19, NEHRU PLACE, NEW DELHI - 110019

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

The present invention relates to a stable pharmaceutical formulation of Lamotrigine and pharmaceutically acceptable acid addition salts thereof. The invention also relates to the preparation of such a formulation.

Lamotrigine is 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine. Lamotrigine is indicated as adjunctive therapy in the treatment of partial seizures in adults with epilepsy.

US Patent No. 5,861,179 describe a powder formulation of Lamotrigine, which comprises lamotrigine or a pharmaceutically acceptable acid addition salt thereof with lactose, starch, crystalline cellulose and polyvinylpyrrolidone.

It further specifies the specific grades, concentrations and particle size of the excipients, which are necessary to make a stable powder formulation. It also discloses the spray granulation process to make such a powder formulation.

The inventors have surprisingly found that stable formulations of Lamotrigine can be prepared by simple process without these stringent particle size and grade requirements. The inventors have discovered that a stable tablet of lamotrigine can be prepared with about 15.5 - 70% of microcrystalline cellulose, about 0.1-14.5% of sodium starch glycolate, about 0.1-4.5% by weight of polyvinylpyrrolidone with or with out lactose by wet granulation.

Therefore, in one general aspect the present invention relates to a tablet of lamotrigine, which comprises:

(a) from about 0.1% to 50 % by weight of lamotrigine or acid addition salt thereof
(b) from about 15.5% to 70% by weight of microcrystalline cellulose
(c) from about 0.1% to 14.5% by weight of sodium starch glycolate
(d) from about 0.1% to 4.5% by weight of polyvinylpyrrolidone

In another general aspect it relates to a tablet of lamotrigine, which comprises:

(a) from about 0.1% to 50 % by weight of lamotrigine or acid addition salt thereof

(b) from about 15.5% to 70% by weight of microcrystalline cellulose
(c) from about 0.1% to 14.5% by weight of sodium starch glycolate
(d) from about 0.1% to 4.5% by weight of polyvinylpyrrolidone
(e) from about 0.1% to 14.5% by weight of lactose

In another general aspect it relates to a process for the preparation of lamotrigine tablets which comprises wet granulating a composition comprising:

(a) from about 0.1% to 50 % by weight of lamotrigine or acid addition salt thereof
(b) from about 15.5% to 70% by weight of microcrystalline cellulose
(c) from about 0.1% to 14.5% by weight of sodium starch glycolate
(d) from about 0.1% to 4.5% by weight of polyvinylpyrrolidone

In another general aspect it relates to a process for the preparation of lamotrigine tablets which comprises wet granulating a composition comprising:

(a) from about 0.1% to 50 % by weight of lamotrigine or acid addition salt thereof
(b) from about 15.5% to 70% by weight of microcrystalline cellulose
(c) from about 0.1% to 14.5% by weight of sodium starch glycolate
(d) from about 0.1% to 4.5% by weight of polyvinylpyrrolidone
(e) from about 0.1% to 14.5% by weight of lactose

The word "about" herein means that the given percentages may vary by ±3.5% of given values. The phrase 'stable formulation' herein refers to a formulation of lamotrigine in which there is no change in assay values, impurity percentage and dissolution data when kept at 40°C/75% RH for 3 months. Lamotrigine raw material and tablets have been reported to have impurities 3-amino-6-(2,3-dichlorophenyl)-1,2,4-triazine-5-(4H)-one (A) and N-(5-amino-6-(2,3-dichloropneyl)-1,2,4-triazine-3-yl)-2,3-dichlorobenzamide (B); wherein the impurity A is a degradation product of lamotrigine produced by hydrolysis of lamotrigine and impurity B is a process impurity formed during the synthesis of lamotrigine.

In the tablets prepared by the process of the invention, the degradation products are either not formed or are below level of quantification.

The microcrystalline cellulose and lactose act as fillers and add to the bulk of the tablet. Sodium starch glycolate is the disintegrant, which can be used intragranularly as well as extragranularly. The polyvinylpyrrolidone acts as a binder.

As used herein lamotrigine refers to its free base or acid addition salt such as methanesulphonate and isothionate salts. Preferred formulations comprise from about 0.1 to about 50% by weight of lamotrigine or a lamotrigine salt by weight of the tablet.

Microcrystalline cellulose is commonly used as filler in tablets. It is a white, odorless, tasteless, free flowing powder. There are various grades available, which differ in bulk density, particle size and moisture content, particularly suitable are Avicel PH101, Avicel PH102, Tabulose® 101, Tabulose®102, Vivapur®102 or a combination thereof. These grades have particle size in the range of about 50μ to about 100μ. Microcrystalline cellulose comprises from about 15.5% to about 70% by weight of tablet, particularly from about 20% to 60%, more particularly from about 20% to 30% by weight of the tablet.

Sodium starch glycolate is used herein as a disintegrant. It is white to off-white, tasteless, odorless, relatively free flowing powder, absorbs water rapidly, resulting in swelling which leads to rapid disintegration of tablets and granules. It can be used as intragranularly as well as extragranularly and comprises about 0.1% to 14.5% by weight of tablet, particularly about 4% to 10% by weight of the tablet.

Polyvinylpyrrolidone is a commonly used binder. It is a white or creamy white powder, available with different molecular weights. Suitable grades include those having molecular weight of from about 40,000 to 1,300,000; particularly suitable are Povidone K30 and Povidone K90 and combinations thereof. Polyvinylpyrrolidone comprises from about 0.1% to 4.5% by weight of the tablet.

Lactose is another commonly used filler in tablets. It is a white or almost white, free flowing powder. Lactose can be anhydrous lactose, particularly suitable are Pharmatose® grades such as, Pharmatose® 150M, 200M, 350M, 450M, DCL21 or a combinations thereof. It comprises from about 0.1% to about 14.5% by weight of tablet, particularly from about 5% to 14.5%, more particularly from about 10-14.5% by weight of the tablet.

Further to this, the tablets may also comprise glidants and lubricants such as talc, colloidal silicon dioxide, magnesium stearate and sodium stearyl fumarate. Generally, these are present in the range of about 0.1% to 2% weight by weight of the tablet.

The tablets are prepared by wet granulation. Lamotrigine or its acid addition salt is mixed with microcrystalline cellulose, sodium starch glycolate, lactose, and polyvinylpyrrolidone. The blend is granulated with purified water in a rapid mixer granulator. Alternatively, a blend comprising lamotrigine or its acid addition salt, microcrystalline cellulose, sodium starch glycolate and lactose is granulated with aqueous solution of polyvinylpyrrolidone. The wet mass is screened to obtain granules. The granules are dried and mixed with extragranular excipients such as fillers like microcrystalline cellulose, disintegrant like sodium starch glycolate, lubricant such as magnesium stearate and glidants like talc and colloidal silicon dioxide and compressed using appropriate tooling.

The following examples are given for purpose of illustrating the present invention and not intended to limit the scope in any way.

EXAMPLE 1

Ingredients	Quantity (mg)
Intragranular	
Lamotrigine	200
Lactose	25
Microcrystalline cellulose	40.5
Sodium Starch Glycolate	16
Polyvinylpyrrolidone	15
Iron oxide (yellow)	0.5
Purified water	q.s
Extragranular	
Microcrystalline cellulose	71
Sodium starch glycolate	24
Magnesium stearate	4
Talc	2
Colloidal silicon dioxide	2
Total	**400**

METHOD

The tablets of example 1 were prepared as follows:

1. Lamotrigine, lactose and polyvinylpyrrolidone and a portion each of microcrystalline cellulose and sodium starch glycolate were sifted through a suitable mesh and mixed for 10 minutes.
2. The blend of Step 1 was granulated with Purified water.
3. The granules were dried in a fluid bed dryer.
4. Sifted colloidal silicon dioxide and the remaining portions of microcrystalline cellulose and sodium starch glycolate through a suitable mesh and mixed with dried granules of step 3.
5. Talc and magnesium stearate were then mixed with the blend of step 4 and compressed using suitable punch tooling.

The tablets of Example 1 were subjected to accelerated studies for three months at 40°C and 75% relative humidity (RH) and the results are shown in Table 1.

Table 1: Stability data of lamotrigine tablets prepared as per example 1 and subjected to accelerated studies.

	Initial	3 Months/40°C/75%RH
Lamotrigine (% w/w)	100.15	99.82
Impurity A (% w/w)	ND*	BLQ**
Total related substances (%w/w)	0.046	0.053

*Not Detected

** Below level of quantification

The tablets of Example 1 were also subjected to dissolution studies in USP 2 apparatus at 50 RPM in 900 mL of 0.1N HCl. The dissolution profile of the tablets at the initial and 3 months period is given in Table 2.

Table 2: Dissolution profile of tablets prepared as per the composition of Example 1 (in USP 2 apparatus at 50 RPM in 900 mL of 0.1N HCl).

Time (min)	% Release	
	Initial	3 months/40°C/75%RH
10	89	90
20	97	99
30	100	101
45	100	104

From tablets of example 1 entire drug content was released within 30 minutes.

EXAMPLE 2

Ingredients	Quantity (mg)
Intragranular	
Lamotrigine	5
Lactose	5.75
Microcrystalline cellulose	15.6
Sodium Starch Glycolate	2.5
Polyvinylpyrrolidone	1.875
Iron oxide (yellow)	0.625
Purified water	q.s
Extragranular	
Microcrystalline cellulose	14.65
Sodium starch glycolate	2.5
Magnesium stearate	0.5
Talc	0.5
Colloidal silicon dioxide	0.5
Total	**50**

METHOD

The tablets of example 2 containing lamotrigine (5mg) were prepared as per the process of example 1 with microcrystalline comprising about 60% by weight of tablet.

EXAMPLE 3

Ingredients	Quantity (mg)
Intragranular	
Lamotrigine	200
Microcrystalline Cellulose	156
Sodium Starch Glycolate	5
Polyvinylpyrrolidone	20
Purified Water	q.s
Extragranular	
Sodium Starch Glycolate	15
Magnesium Stearate	2
Colloidal Silicon Dioxide	2
Total	**400**

METHOD

The tablets of example 3 containing lamotrigine (5mg) were prepared as per the processes of examples 1 and 2 without lactose.

The tablets of Example 3 were subjected to accelerated studies for three months at

40°C and 75% relative humidity and the results are shown in Table 3.

Table 3: Stability data of lamotrigine tablets prepared as per example 3 and subjected to accelerated studies.

	Initial	3 Months/40°C/75%RH
Lamotrigine (% w/w)	99.67	99.43
Impurity A (% w/w)	ND*	BLQ**
Total related substances (%w/w)	0.043	0.054

*Not Detected

** Below level of quantification

The dissolution profile of the tablets of example 3 was measured in USP 2 apparatus at 50 RPM in 900 mL of 0.1N HCl. The dissolution profile of the tablets at the initial and 3 months period is given in Table 4.

Table 4: Dissolution profile of tablets prepared as per the composition of Example 1 (in USP 2 apparatus at 50 RPM in 900 mL of 0.1N HCl).

Time (min)	% Release	
	Initial	3 months/40°C/75%RH
10	88	81
20	97	97
30	100	92
45	101	102

From tablets of example 3 entire drug content was released within 45 minutes.

WE CLAIM:

1. A process for preparation of lamotrigine tablet which comprises wet granulating a composition comprising:

   from about 0.1% to 50 % by weight of lamotrigine or acid addition salt thereof;

   from about 15.5% to 70% by weight of microcrystalline cellulose;

   from about 0.1% to 14.5% by weight of sodium starch glycolate and

   from about 0.1% to 4.5% by weight of polyvinylpyrrolidone.

2. The process according to claim 1 wherein the tablet further comprises from about 0.1% to 14.5% by weight of lactose.

3. The process according to claim 1 wherein the tablet comprises about 50% by weight of lamotrigine, about 20% to 60% by weight of microcrystalline cellulose, about 4% to 10% by weight of sodium starch glycolate and about 0.1% to 4.5% by weight of polyvinylpyrrolidone.

4. The process according to claim 2 wherein the tablet comprises about 10% by weight of lamotrigine, about 20% to 60% by weight of microcrystalline cellulose, about 5% to 14.5% by weight of lactose, about 4% to 10% by weight of sodium starch glycolate and about 0.1% to 4.5% by weight of polyvinylpyrrolidone.

5. The process according to claim 2 wherein the tablet comprises about 50% by weight of lamotrigine, about 20% to 30% by weight of microcrystalline cellulose, about 10% to 14.5% by weight of lactose, about 4% to 10% by weight of sodium starch glycolate and about 0.1% to 4.5% by weight of polyvinylpyrrolidone.

6. The process according to claim 1 or 2 wherein lamotrigine or its acid addition salt, microcrystalline cellulose, sodium starch glycolate, polyvinylpyrrolidone and/or lactose are blended and the blend is granulated with water.

7. The process according to claim 1 or 2 wherein lamotrigine or its acid addition salt, microcrystalline cellulose, sodium starch glycolate and/or lactose are blended and the blend is granulated with aqueous solution of polyvinylpyrrolidone.

8. The process according to claim 6 or 7 wherein further to granulation, wet mass is screened to obtain granules.

9. The process according to claim 8 wherein the granules are dried.

10. The process according to claim 9 wherein dried granules are sieved.

11. The process according to claim 10 wherein the granules are compressed to form tablets.

12. The process according to claim 1 wherein sodium starch glycolate is intragranular.

13. The process according to claim 1 wherein sodium starch glycolate is extragranular.

14. A process for the preparation of lamotrigine tablet substantially described and exemplified herein.

Dated this 21ST day of **March, 2003.**

For RANBAXY LABORATORIES LIMITED

(Sushil Kumar Patawari)
Company Secretary

ABSTRACT

The present invention relates to a process for the preparation of stable pharmaceutical formulation of Lamotrigine and pharmaceutically acceptable acid addition salts thereof.